

A20
mp
5/1/23

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : S. Charbit et al.
Serial No. : 09/768816
Filed : 1/23/01
For : TREATMENT OF PATHOLOGICAL
CONDITIONS CHARACTERIZED
BY AN INCREASED IL-1 LEVEL
Attorney
Docket No. : H7708-0002
Examiner : Mojdeh Bahar
Art Unit : 1617

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

Declaration Of Diego Provvedini Under 37 C.F.R. § 1.132

I, Diego Provvedini, M.D., declare and say that:

My residence address is: 55 Rue Jacques Kellner, 78380 Bougival, France.

I am a Physician trained in Italy and the United States in basic and clinical research focusing on the musculoskeletal system, and currently employed in the pharmaceutical industry in France. A copy of my Curriculum Vitae is attached hereto as Exh. A.

I understand the treatment of pathological conditions characterized by an increased IL-1 and/or TNF- α level through the administration of diacerein and/or rhein, as disclosed and claimed in the above-identified patent application.

I have reviewed the above-identified patent application disclosure and the prior art references cited by the Examiner in the Office Action, namely the Martel-Pelletier et al. reference and the Marcolongo et al. reference.

A person of ordinary skill in this particular field would not have been motivated to combine the *in vitro* results of Martel-Pelletier et al. with Marcolongo's symptomatic treatment regimen and the statements on page 1 of the patent application, and have a reasonable expectation that an underlying pathological cause of the claimed group of diseases would be successfully treated. As a general matter, it is not possible to link *in vitro* observations of the effectiveness of a drug with other results independently observed *in vivo* in another study. The clinician of ordinary skill very often observes that several mechanisms are involved in the expression of a pathologic condition in a patient. Thus, even in the *in vitro* systems that most closely model *in vivo* conditions, these same mechanisms are not necessarily present and/or involved, due to many possible reasons such as a lack of critical components and elements, or the insufficiency of the observation times. Furthermore, in *in vivo* testing the deficit of one mechanism can be compensated by others, thereby maintaining an overall balanced situation. These homeostatic and compensatory mechanisms may further explain the absence of a correlation between the *in vitro* versus the *in vivo* effectiveness of a drug that is very often observed during pharmacological development.

The matrix metalloprotease (MMP) inhibitors represent a good example of the existence of the "disconnect" between *in vitro* versus *in vivo* data. Considerable efforts have been made to produce MMP inhibitors as therapeutic agents for chondro-destructive pathologies. Thus, several MMP inhibitors have entered clinical trials, but have never reached the market. The most recent example is Roche's *Trocade*, a selective inhibitor of collagenase (MMP-1 and -

3, and, at least in part, -13 and -14) which had been extensively tested in pre-clinical settings, but whose development was terminated after a phase III study in rheumatoid arthritis (RA) showed no effect whatsoever. The explanation for the failure of *Trocade*, a powerful MMP inhibitor *in vitro*, is not known. This is even more intriguing in view of the fact that an antagonist of MMPs, the tissue inhibitor of metalloprotease (TIMP), can completely block the destruction of the collagen induced *in vitro* by the MMPs.

A similar example of the "disconnect" between *in vitro* versus *in vivo* data is represented by the statins, powerful cholesterol-lowering agents. Considerable enthusiasm had been generated by the observation of their beneficial effects on bone metabolism, which induced to propose them as a potential treatment for bone-losing pathologies, and osteoporosis in particular. Their promising *in vitro* effect on the enzyme HMG-CoA reductase and the maturation of the bone-resorbing osteoclasts has not been confirmed *in vivo* during several large, controlled clinical trials. Therefore, at the present time statins are no longer considered as a viable alternative treatment for osteoporosis.

Another very clear and fitting example of the existence of a disconnect between *in vitro* versus *in vivo* data is represented by the involvement of the cytokine IL-1 in the mechanisms of the immune response. Indeed, a large body of *in vitro* experimental evidence has demonstrated beyond doubt that IL-1 plays a pivotal role in the activation of the immune cells during their response to an immune stimulus. Thus, it is logical to believe that the inhibition of the production, levels or activity of this cytokine would have some effect on an immune response *in vivo*. Nevertheless, in a total population of more than 3,000 patients receiving diacerein during controlled clinical trials no inhibitory effect on immunity due to the inhibition of IL-1 was ever demonstrated.

It needs to be pointed out that the IL-1 system is very complex (*Arend W P and Guthridge C J: Biological role of interleukin 1 receptor antagonist isoforms. Ann Rheum Dis 2000; 59 (suppl 1): 160 -4*, attached as Exh. B): there are at least 2 ligands (IL-1 α and IL-1 β) and at least 2 receptors (IL-1RI and IL-1RII). In addition, the main IL-1 antagonists are represented by one secreted form (called sIL-1Ra), produced by monocytes and macrophages, and three different intracellular isoforms, whose biological role is still unclear, namely: 1) icIL-1Ra1 (a major protein in keratinocytes and other epithelial cells); 2) icIL-1Ra2 (in neutrophils, fibroblasts, keratinocytes and myelomonocytic cells); and 3) icIL-1Ra3 (a major protein in hepatocytes and neutrophils, and in smaller amounts in monocytes, macrophages and keratinocytes). The effect of a drug or treatment on IL-1 might therefore depend upon several different actions on various elements of this cytokine's homeostatic system, such as the interleukin-converting enzyme (ICE), the receptor(s), the antagonist(s), or directly on the IL-1 molecule itself.

Thus, it is clear that the field of art in the above-identified application is particularly complex and highly unpredictable so that a person of ordinary skill could not reasonably conclude that the same effects observed *in vitro* would be obtained when diacerein is administered *in vivo*.

I am also familiar with the data underlying, and the work surrounding, the Martel-Pelletier et al. reference. In my opinion, as stated above, the highly complex nature of this field would preclude one of ordinary skill in the art from making any reasonable predictions that diacerein or rhein would prevent the progression of osteoarthritis in humans when administered to humans based only on the reported *in vitro* results of the paper. The authors themselves apparently understood that they needed to see the results of the human trials before assessing the

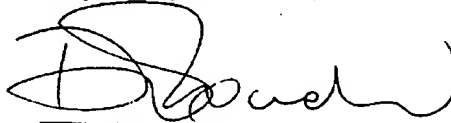
clinical relevance of the *in vitro* results in their paper, and therefore did not have an expectation that the *in vitro* model would necessarily correlate with a positive clinical outcome. Indeed, for this purpose, they stated in their paper: "Diacerein is currently under investigation *in vivo* in patients with hip and knee osteoarthritis to explore its potential structure modifying effect. The latter should yield useful information regarding the clinical relevance of this *in vitro* study." Of course they may have been hopeful that the *in vitro* results would carry over to the *in vivo* results, but they expressed no reasonable expectation that their *in vitro* results would do so.

Based on my reading of the above-identified patent application, one of ordinary skill in the art would understand that pulmonary fibrosis would be included within the group of inflammatory and autoimmune diseases described in the application. First, one of ordinary skill in the art would have known that pulmonary fibrosis is an inflammatory disease of the lungs characterized by increased IL-1 and TNF- α levels. Second, the application contains multiple references to inflammatory diseases characterized by increased IL-1 and TNF- α levels. For example, p. 1, lns. 10-11 ("The invention specifically resides in a method for treatment of pathological conditions characterized by an increased IL-1 and/or TNF- α level..."), p. 6, lns. 14-17 ("An objective of the invention was to provide a method of treatment [for] patients suffering from the inflammatory and autoimmune diseases, in which inflammatory cytokines, such as interleukin-1 (IL-1) and tissue necrosis factor α (TNF- α) are present to an increased degree..."), claim 1 as originally filed ("Method of treating pathological conditions characterized by an increased IL-1 and/or TNF- α level...") and claim 11 as originally filed ("Method of treating inflammatory and autoimmune conditions characterized by an increased IL-1 and/or TNF- α level..."). Furthermore, the specification throughout states that "the pathological conditions contemplated herein ... broadly encompass the inflammatory and autoimmune diseases" (p. 1,

lns. 18-19), "the use of diacerein and rhein in the treatment of inflammatory and autoimmune diseases" (p. 4, ln. 7), "method of treatment including the administration of diacerein or rhein to patients suffering from the inflammatory and autoimmune diseases" (p. 6, ln. 14-16), Claim 2, etc. Attention is also called to p. 5, lns. 17-18, wherein it is noted that "IL-1 and TNF... contribute to the fibrosis and tissue degeneration of the chronic proliferative phase of inflammation" (emphasis added). Based on these disclosures in the application, I conclude that one of ordinary skill in the art would recognize from the disclosure that the application contains an adequate description of the general group of diseases characterized by increased IL-1 and TNF- α levels such as to lead one of ordinary skill in the art to understand that pulmonary fibrosis is included within this group.

I declare further that all statements made herein of my own knowledge are true, and that all statements made on information are believed to be true; and, further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully Submitted,



Diego Provvedini

Dated: September 17, 2002

FEB 04 2003

A Division of The McGraw-Hill Companies
PATENT & TRADEMARK OFFICE

RECEIVED
FEB 06 2003
TECH CENTER 1600/2900

Note: Dr. Fauci and Dr. Longo's works as editors and authors were performed outside the scope of their employment as U.S. government employees. These works represent their personal and professional views and not necessarily those of the U.S. government.

Harrison's
PRINCIPLES OF INTERNAL MEDICINE
Fourteenth Edition

Copyright © 1998, 1994, 1991, 1987, 1983, 1980, 1977, 1974, 1970, 1966, 1962, 1958 by *The McGraw-Hill Companies, Inc.* All rights reserved. Printed in the United States of America. Except as permitted under the United States Copyright Act of 1976, no part of this publication may be reproduced or distributed in any form or by any means, or stored in a data base or retrieval system, without the prior written permission of the publisher.

1234567890 DOWDOW 9987
ISBN 0-07-020291-5 (COMBO)
0-07-020292-3 (VOL. 1)
0-07-020293-1 (VOL. 2)
0-07-912013-X (SET)

FOREIGN LANGUAGE EDITIONS

Arabic (Thirteenth Edition)—McGraw-Hill Libri Italia srl (est. 1996)
Chinese (Twelfth Edition)—McGraw-Hill Book Company—Singapore © 1994
Croatian (Thirteenth Edition)—McGraw-Hill Libri Italia srl (est. 1996)
French (Thirteenth Edition)—McGraw-Hill Libri Italia srl © 1995
German (Thirteenth Edition)—McGraw-Hill Libri Italia srl © 1995
Greek (Twelfth Edition)—Parissianos © 1994
Italian (Thirteenth Edition)—McGraw-Hill Libri Italia srl © 1995
Japanese (Eleventh Edition)—Hirokawa © 1991
Portuguese (Thirteenth Edition)—McGraw-Hill/Nueva Editorial Interamericana © 1995
Spanish (Thirteenth Edition)—McGraw-Hill Interamericana de España © 1994
Turkish (Thirteenth Edition)—McGraw-Hill Libri Italia srl (est. 1996)

This book was set in Times Roman by Monotype Composition Company. The editors were J. Dereck Jeffers, Martin J. Wonsiewicz, and Mariapaz Ramos Englis; editorial assistants were Rose Derario and Daniel J. Green. The production director was Robert Latfler. The index was prepared by Irving Tullar. The text and cover designer was Marsha Cohen/Parallelogram Graphics.

R.R. Donnelley and Sons, Inc., was the printer and binder.

Library of Congress Cataloging-in-Publication Data

Harrison's principles of internal medicine.—14th. ed./editors.
Anthony S. Fauci . . . [et al.]

p. cm.

Includes bibliographical references and index.

ISBN 0-07-020291-5 (1 vol. ed.).—ISBN 0-07-912013-X (2 vol. ed.

: set).—ISBN 0-07-020292-3 (2 vol. ed. : bk 1).—ISBN

0-07-020293-1 (2 vol. ed. : bk 2)

I. Internal medicine. I. Harrison, Tinsley Randolph.

II. Fauci, Anthony S.

[DNLM: 1. Internal Medicine. WB 115 H322 1998]

RC46.H333 1998

616—dc21

DNLM/DLC

for Library of Congress

BEST AVAILABLE COPY

97-14184

half-life, prednisone is the drug of choice except in infants, in whom hydrocortisone is usually used. In adults with late-onset adrenal hyperplasia, the smallest single bedtime dose of a long- or intermediate-acting glucocorticoid that suppresses pituitary ACTH secretion should be administered. The amount of steroid required by children with congenital adrenal hyperplasia is approximately 1 to 1.5 times the normal cortisol production rate of 27 to 35 μmol (10 to 13 mg) of cortisol per square meter of body surface per day and is given in divided doses two or three times per day. The dosage schedule is governed by repetitive analysis of the urinary 17-ketosteroids, plasma DHEA sulfate, and/or precursors of cortisol biosynthesis. Skeletal growth and maturation also must be monitored closely, since overtreatment with glucocorticoid replacement therapy retards linear growth.

Table
Laboratory Evaluation of Hirsutism-Virilizing Syndromes

	Ovarian		Adrenal			
	PCO	Ovarian Tumor	CAH	Adrenal Neoplasm	Cushing's Syndrome	Idiopathic
Urinary 17-ketosteroids, plasma DHEA sulfate	N↑	N	N↑	↑↑↑	N↑	N
Plasma testosterone	N↑	↑↑	N↑	N↑	N↑	N
LH/FSH ratio	N↑	N	N	N	N	N
Precursors of cortisol biosynthesis:						
Basal	N	N	N↑	N↑	N	N
Following ACTH infusion	N	N	↑↑	N↑	N	N
Cortisol following overnight dexamethasone suppression test	N	N	N	↑	↑	N

NOTE: CAH, congenital adrenal hyperplasia; PCO, polycystic ovary syndrome; N, normal; ↑, elevated.

HYPOFUNCTION OF THE ADRENAL CORTEX

Cases of adrenal insufficiency can be divided into two general categories: (1) those associated with primary inability of the adrenal to elaborate sufficient quantities of hormone and (2) those associated with a secondary failure due to inadequate ACTH formation or release (Table 332-9).

PRIMARY ADRENOCORTICAL DEFICIENCY (ADDISON'S DISEASE) The original description of Addison's disease—"general languor and debility, feebleness of the heart's action, irritability of the stomach, and a peculiar change of the color of the skin"—summarizes the dominant clinical features. Advanced cases are usually easy to diagnose, but recognition of the early phases can be a real challenge.

Incidence Primary insufficiency is relatively rare, may occur at any age, and affects both sexes equally. Because of the common therapeutic use of steroids, secondary adrenal insufficiency is relatively common.

Etiology and Pathogenesis Addison's disease results from progressive destruction of the adrenals, which must involve more than 90 percent of the glands before adrenal insufficiency appears. The adrenal is a frequent site for chronic granulomatous diseases, predominantly tuberculosis but also histoplasmosis, coccidioidomycosis, and cryptococcosis. In early series, tuberculosis was responsible for 70 to 90 percent of cases, but the most frequent cause now is *idiopathic* atrophy, and an autoimmune mechanism is probably responsible. Rarely, other lesions are encountered, such as adrenoleukodystrophy, bilateral hemorrhage, tumor metastases, amyloidosis, adrenomyeloneuropathy, familial adrenal insufficiency, or sarcoidosis.

Half of patients have circulating adrenal antibodies. Specific adrenal antigens to which autoantibodies may be directed include P450_{C21}. While most antibodies cause adrenal destruction, some antibodies cause adrenal insufficiency by blocking the binding of ACTH to its receptors. Some patients also have antibodies to thyroid, parathyroid, and/or gonadal tissue (see also Chap. 340). There is also an increased incidence of chronic lymphocytic thyroiditis, premature ovarian failure, type I diabetes mellitus, and hypo- or hyperthyroidism. The presence of two or more of these autoimmune endocrine disorders in the same person defines the polyglandular autoimmune syndrome type II. Additional features include pernicious anemia, vitiligo, alopecia, nontropical sprue, and myasthenia gravis. Within families, multiple generations are affected by one or more of the above diseases. Type II polyglandular syndrome is the result of a mutant gene on chromosome 6 and is associated with the HLA alleles B8 and DR3.

The combination of parathyroid and adrenal insufficiency and chronic mucocutaneous moniliasis constitutes type I polyglandular autoimmune syndrome. Other autoimmune diseases in this disorder

include pernicious anemia, chronic active hepatitis, alopecia, primary hypothyroidism, and premature gonadal failure. There is no HLA association; this syndrome is inherited as an autosomal recessive trait. The type I syndrome usually presents during childhood, whereas the type II syndrome is usually manifested in adulthood. The mechanisms by which genetic predisposition and/or autoimmunity interact in the pathogenesis of these disorders are unknown.

Clinical suspicion of adrenal insufficiency should be high in patients with AIDS (see Chap. 308). Cytomegalovirus regularly involves the adrenal glands [so-called cytomegalovirus (CMV) necrotizing adrenalitis], and involvement with *Mycobacterium avium-intracellulare*, *Cryptococcus*, and Kaposi's sarcoma has been reported. Adrenal insufficiency in AIDS patients may not be manifest, but tests of adrenal reserve frequently give abnormal results. When interpreting tests of adrenocortical function, it is important to remember that medications such as rifampin, phenytoin, ketoconazole, and opiates may cause or potentiate adrenal insufficiency.

Adrenoleukodystrophy causes severe demyelination and early death in children, and adrenomyeloneuropathy is associated with a mixed motor and sensory neuropathy with spastic paraplegia in adults; both disorders are associated with elevated circulating levels of very long chain fatty acids and cause adrenal insufficiency. Familial adrenal insufficiency is an autosomal recessive disorder that causes unresponsiveness to ACTH secondary to mutations in the ACTH receptor. Adrenal hemorrhage and infarction occur in patients on anticoagulants and in those with circulating anticoagulants and hypercoagulable states, such as the antiphospholipid syndrome.

Clinical Signs and Symptoms Adrenocortical insufficiency caused by gradual adrenal destruction is characterized by an insidious onset of fatigability, weakness, anorexia, nausea and vomiting, weight

Table 332-9

Classification of Adrenal Insufficiency

PRIMARY ADRENAL INSUFFICIENCY

- Anatomic destruction of gland (chronic or acute)
 - "Idiopathic" atrophy (autoimmune, adrenoleukodystrophy)
 - Surgical removal
 - Infection (tuberculous, fungal, viral—especially in AIDS patients)
 - Hemorrhage
 - Invasion: metastatic
- Metabolic failure in hormone production
 - Congenital adrenal hyperplasia
 - Enzyme inhibitors (metyrapone, ketoconazole, aminoglutethimide)
 - Cytotoxic agents (mitotane)
 - ACTH-blocking antibodies
 - Mutation in ACTH receptor gene

SECONDARY ADRENAL INSUFFICIENCY

- Hypopituitarism due to hypothalamic-pituitary disease
- Suppression of hypothalamic-pituitary axis
 - By exogenous steroid
 - By endogenous steroid from tumor



EXHIBIT C

A list of selected citations of idiopathic diseases on the internet

RECEIVED
FEB 06 2003
TECH CENTER 1600/2900

Hematological disorders:

Idiopathic Thrombocytopenia Purpura

<http://www.medical-library.net/medical-library/Idiopathic-Thrombocytopenia-Purpura-%28-ITP%29.htm>

ACP-ASIM Online - Idiopathic Thrombocytopenic Purpura

From the Am. College of Physicians - Am. Society of Internal Medicine.

www.acponline.org/journals/annals/01oct97/letter2.htm

eMedicine.com - Idiopathic Thrombocytopenic Purpura

Complete diagnosis and treatment details, follow-up details and a bibliography.

www.emedicine.com/emerg/topic282.htm

Disorders of the cardiovascular system:

American Family Physician - Idiopathic Pericardial Effusion

Reveals the results of a study of patients with the cardiac disorder pericarditis.

www.findarticles.com/cf_dls/m3225/10_61/62829173/p1/article.jhtml

Disorders of the respiratory system:

Pharmacological Therapy for Idiopathic Pulmonary Fibrosis Past, Present, and Future - NHLBI Workshop Summary, published in the Am J Respir Crit Care Med Vol 160. pp 1771- 1777, 1999

www.pulmonaryfibrosis.org/workshop.htm

Disorders of the kidney and urinary tract:

Treatment of idiopathic nephrotic syndrome in children

nephrotic-syndrome.org/disease/treatment.html

idiopathic nephrotic syndrome and hexadactyly in two brothers

link.springer.de/link/service/journals/00467/bibs/8012005/80120417.htm

Idiopathic Primary Renal Hematuric/Proteinuric Synd. - GEM

Group of disorders marked by blood and protein in the urine and damage to the kidney.

www.findarticles.com/cf_dls/g2601/0007/2601000734/p1/article.jhtml

Disorders of the gastrointestinal system:

the Gastrolab IMAGE Gallery - Nongranulomatous Chronic Idiopathic Enterocolitis

Pictures from the rectum and colon in a patient

www.gastrolab.net/g4non.htm

Gastroenterology - Idiopathic Autoimmune Chronic Hepatitis

A good, though brief (less than 1024 chars), description of your site.

www.mc.vanderbilt.edu/peds/pidl/gi/chrhepa.html

Disorders of the immune system, connective tissue and joints:

Clarinex

Info on Clarinex (desloratadine) indicated for rhinitis and chronic idiopathic urticaria.

www.clarinexinfo.com

Dermatology Times - Fexofenadine Drops Number of Wheals

Study examines the efficacy of fexofenadine for patients with chronic idiopathic urticaria.

www.findarticles.com/cf_dls/m0UMR/2_21/59736376/p1/article.jhtml

1UpHealth - Sarcoidosis (Hutchinson's Disease or Boeck's Disease)

Explore this idiopathic systemic inflammatory granulomatous disorder that may affect lungs, lymph nodes, skin, liver, spleen, eyes, phalangeal bones, and parotid glands.

www.1uphealth.com/medical/disease/immune-disease/sarcoidosis-1.html

Endocrinology and Metabolism:

idiopathic type 1 diabetes in dallas, texas: a 5-year experience

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11375362&dopt=Abstract

Doctor's Guide - Geref

Learn about Geref, used to treat idiopathic growth hormone deficiency (GHD).

www.pslgroup.com/dg/6f152.htm

idiopathic hypoparathyroidism

Document about idiopathic hypoparathyroidism

chorus.rad.mcw.edu/doc/00932.html

Harvard Radiology Center Resource

Descriptions and an X-ray of six-month-old female with idiopathic pulmonary hemosiderosis.

brighamrad.harvard.edu/Cases/mcr/hcache/237/full.html

Idiopathic Hepatic Lipidosis - Max's House

Article about this serious liver condition outlines its many causes. Learn about treatment.

maxshouse.com/idiopathic_hepatic_lipidosis.htm

Adolescent Idiopathic Scoliosis: Review and Current Concepts - July 1, 2001 - American Family Physician Family Practice | Adolescent Idiopathic Scoliosis: Review and Current Concepts

www.aafp.org/afp/20010701/111.html

Diffuse Idiopathic Skeletal Hyperostosis (D.I.S.H.)
What is Diffuse Idiopathic Skeletal Hyperostosis (D.I.S.H.)?
orthopedics.about.com/library/glossary/bldef-dish.htm

Neurologic disorders:

BMJ - Prevalence of Idiopathic Parkinson's Disease
Survey looks at the incidence of Parkinson's disease and related syndromes.
www.findarticles.com/cf_dls/m0999/7252_321/63713363/p1/article.jhtml

Online Mendelian Inheritance in Man - Idiopathic
Generalized idiopathic epilepsy.
www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispim?600669

Univ. of Iowa - Idiopathic Intracranial Hypertension
Defines pseudotumor cerebri and traces the causes of the condition.
webeye.ophth.uiowa.edu/dept/iih/pc_index.htm

Digital Journal of Ophthalmology - Pseudotumor Cerebri
Covers this disease, also known as idiopathic intracranial hypertension, in a Q&A format.
www.djo.harvard.edu/meei/PI/pseudotcereb.html

Handbook of Ocular Disease Management - Idiopathic Central Serous Chorioretinopathy
Patients with idiopathic central serous chorioretinopathy (ICSC).
www.revoptom.com/handbook/sect5m.htm



Idiopathic Pulmonary Fibrosis

What is Idiopathic Pulmonary Fibrosis?

Idiopathic Pulmonary Fibrosis (IPF) is a disease of inflammation that results in scarring, or fibrosis, of the lungs. In time, this fibrosis can build up to the point where the lungs are unable to provide oxygen to the tissues of the body.

Doctors use the word "idiopathic" (from the Greek "idio" meaning "peculiar" or "unusual" and "pathy" meaning "illness") to describe the disease, because the cause of IPF is unknown. Currently, researchers believe that IPF may result from either an autoimmune disorder, a condition in which the body's immune system attacks its own tissues, or the after effects of an infection, most likely a virus.

EXD

Whatever the trigger is for IPF, it appears to set off a series of events in which the inflammation and immune activity in the lungs -- and, eventually, the fibrosis processes, too--become uncontrollable. In a few cases, heredity appears to play a part, possibly making some individuals more likely than others to get IPF.

In studies of patients with IPF, the average survival rate has been found to be 4 to 6 years after diagnosis. Those who develop idiopathic pulmonary fibrosis at a young age seem to have a longer survival.

Who Gets IPF

The exact number of people who develop idiopathic pulmonary fibrosis each year is not known. It is known, however, that equal numbers of men and women get the illness and that most cases of IPF are diagnosed when the patients are between the ages of 40 and 70.

Symptoms

Early symptoms of idiopathic pulmonary fibrosis are usually similar to those of other lung diseases. Very often, for example, patients suffer from a dry cough and dyspnea (shortness of breath). As the disease progresses, dyspnea becomes the major problem. Day-to-day activities such as climbing stairs, walking short distances, dressing, and even talking on the phone and eating become more difficult and sometimes nearly impossible. Enlargement (clubbing) of the fingertips may develop. The patient may also become less able to fight infection. In advanced stages of the illness, the patient may need oxygen all the time.

IPF can lead to death. Often the immediate cause is respiratory failure due to hypoxemia, right-heart failure, a heart attack, blood clot (embolism) in the lungs, stroke, or lung infection brought on by the disease.

The Course Of IPF

Although the course of idiopathic pulmonary fibrosis varies greatly from person to person, the disease usually develops slowly, sometimes over years.

The early stages are marked by alveolitis, an inflammation of the air sacs called alveoli, in the lungs. The job of the air sacs is to allow the transfer of oxygen from the lungs into the blood and the elimination of carbon dioxide from the lungs and out of the body.

As IPF progresses, the alveoli become damaged and scarred, thus stiffening the lungs. The stiffening makes breathing difficult and brings on a feeling of breathlessness (dyspnea), especially during activities that require extra effort.

In addition, scarring of the alveoli reduces the ability of the lungs to transfer oxygen. The resulting lack of oxygen in the blood (hypoxemia) may cause increases in the pressure inside the blood vessels of the lungs, a situation known as pulmonary hypertension. The high blood pressure in the lungs then puts a strain on the right ventricle, the lower right side of the heart, which pumps the oxygen-poor blood into the lungs.

How IPF is Diagnosed

The first suspicion that a person may have idiopathic pulmonary fibrosis is usually based on the patient's symptoms and medical history. The doctor will try to confirm or rule out any suspicion by ordering one or more of the following tests:

Chest x-ray

A simple chest x-ray is a picture of the lungs and surrounding tissues, most often taken while the patient is standing up. In an IPF patient, the x-ray usually reveals shadows, mostly in the lower part of the lungs. In addition, lung size tends to appear smaller than normal.

Computed Tomography (CT)

A computed tomography scan of the chest is a series of x-rays that provide a view of the lungs that looks almost as if a slice had been made through the chest. During a CT scan, the patient lies inside a long, oval-shaped machine that permits x-ray beams to pass through the top, sides, and back of the body. A computer is used to combine all the pictures taken from these positions and thus gives the doctor a good look at what's going on inside the lungs and chest.

Blood Tests

When IPF is suspected, the doctor will analyze the patient's blood. A low level of oxygen in the arterial blood may reveal that the alveoli are not taking up enough oxygen.

Pulmonary Function Tests

Pulmonary function tests (PFTs) require the patient to breathe into a mouthpiece. The mouthpiece, in turn, is connected to a machine that measures the amount of air the patient breathes in and out over a specific period of

time. The results tell the doctor how well the air passages in the lungs are functioning and how well the lungs are expanding.

Bronchoalveolar Lavage

Lung washings (bronchoalveolar lavage) are also helpful in arriving at a diagnosis of IPF. In this procedure, the doctor inserts a long, narrow, flexible, lighted tube called a bronchoscope down the windpipe and into the lungs to remove fluid (lavage) and other materials from inside the lungs.

Even if some or all of the results from such tests are abnormal, they are rarely sufficient to make a specific diagnosis of IPF. The only way the doctor can confirm a diagnosis of IPF is by examining the lung tissue; such tissue is usually obtained by an open lung biopsy.

Open Lung Biopsy

In an open lung biopsy, a chest surgeon makes cuts between the ribs in the chest and removes small pieces of tissue from several places in the lungs. The material is examined in the laboratory to determine how much inflammation and fibrosis are in the lungs. It is the only way to confirm whether the patient has IPF. If IPF is present, the biopsy results are also the best way to find out how far the disease has progressed and what the outlook is.

In a patient with no other significant illness, recovery from an open lung biopsy is relatively quick. The hospital stay is usually 4 to 7 days; some newer procedures require less surgery, bringing hospital stays to 1 to 3 days.

Treatment

The best chance of slowing the progress of IPF is by treatment as soon as possible. Most IPF patients require treatment throughout life, usually under the guidance of a lung specialist. Some major medical centers and large teaching hospitals do research on the disease and provide consultation and treatment to patients.

Treatment for idiopathic pulmonary fibrosis may vary a great deal. It depends on many things, including the age of the patient and stage of the disease. The aim of treatment is to reduce the inflammation of the alveoli and stop the abnormal process that ends in fibrosis. Once scar tissue has formed in the lung, it cannot be returned to normal.

Drugs are the primary way that IPF is treated. They are usually prescribed for at least 3 to 6 months. This gives the doctor time to see if a particular treatment is effective. A combination of tests is used to monitor how well a particular drug is working. The dose may have to be adjusted so that the medicine gives the best

possible results with the least side effects. Most side effects are reduced when the dose is made smaller or the drug is stopped. Commonly used drugs are prednisone and cytoxan. Oxygen administration and, in special cases, transplantation of the lung are other choices.

Prednisone

A corticosteroid, prednisone, is the most common drug given to patients with idiopathic pulmonary fibrosis. About 25 to 35 percent of all patients respond favorably to this medicine. No one knows exactly how corticosteroids work or why some patients do well on prednisone while others do not. Patients take prednisone by mouth every morning, starting with a high dose for the first 4 to 8 weeks. As they improve, they gradually take smaller amounts. Changes in mood are one of the more common side effects of prednisone; most patients, however, can handle the mood changes -- anxiety, depression, or sleeplessness -- once they know what is causing the problem. A less common side effect is a rise in blood-sugar levels, osteoporosis, high blood pressure, cataracts, and increased susceptibility to infection.

Cytosan

Cyclophosphamide, also referred to as cytosan, may be taken together with prednisone, or instead of it. Like prednisone, cytosan is swallowed each day.

One of the more serious side effects of cyclophosphamide is leukopenia, a condition in which the number of white blood cells drops to a dangerously low level. Leukopenia can be controlled by regularly checking the blood count and adjusting the dose of cytosan if necessary.

Other Medicines

Azathioprine, penicillamine, chlorambucil, vincristine sulfate, and colchicine have been used in a few patients with idiopathic pulmonary fibrosis. The newer treatments use drugs which are still in phase two trials such as: interferon-gamma 1b, and an antifibrotic agent, pirfenidone.

Oxygen

In addition to treatment with medicine, some patients may need oxygen, especially when blood oxygen becomes low. This treatment helps re-supply the blood with oxygen. As a result, breathlessness is reduced, the patient can be more active, and the severity of pulmonary hypertension decreases.

Exercise

Regular exercise may be useful for patients with IPF. A daily walk or regular use of a stationary bicycle or

treadmill can improve muscle strength and breathing ability and also increase overall strength. If needed, supplemental oxygen should be used; sometimes it is the only way a patient is able to do a reasonable amount of activity.

Lung Transplantation

Lung transplantation, either of both lungs or only one, is an alternative to drug treatment for patients in the severe, final stages of IPF. It is most often performed in patients under 60 years of age who do not respond to any form of treatment. The survival rate is approximately 60 percent.

Lifestyle

Many IPF patients, particularly those in the early stages of the disease, respond to drug treatment and can continue to go about most of their normal activities, including working. Some patients with advanced IPF need to carry oxygen with them.

In addition to getting proper treatment, IPF patients can help themselves by following the same sensible health measures that everyone should observe. These include eating a healthy diet, maintaining proper weight, exercising regularly, and getting enough rest. Above all, IPF patients should not smoke. Pregnancy is not advisable because the illness puts an extra load on the heart and lungs.

As with many chronic illnesses, emotional support and psychological counseling can be of much help to the patient. Most doctors and patients agree that it is important for both patient and family to be as informed as possible about IPF. In this way, everyone involved can understand the illness and apply that information to what is happening in his or her own life.

Source: the above content is a public domain document: NIH Publication No. 95-2997, "Idiopathic Pulmonary Fibrosis," September 1995.

Information on this web site is provided for informational purposes only and is not a substitute for professional medical advice. You should not use the information on this web site for diagnosing or treating a medical or health condition. If you have or suspect you have a medical problem, promptly contact your professional healthcare provider.

**[Click here for information
on current research and the
latest treatments for IPF](#)**